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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	
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07/07/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/678,723	**Applicant(s)** MARBAN ET AL.
	Examiner David Montanari	**Art Unit** 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,20-34,42,46-48 and 77-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 20-34, 42, 46-48 and 77-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/2010 has been entered.

1. Claims 1, 20-22, 29, 31-34, 42 and 46-48 are amended.
2. Claims 84-88 are new.
3. Claims 5, 7-19, 35-41, 43-45 and 49-76 are cancelled.
4. The rejection of claims 1-4, 6, 20-34, 42, 46-48 and 77-82 under 35 USC 112, first parag., written description, is withdrawn in view of Applicant cancelling the variant language of the claims.
5. The rejection of claims 2-4, 6 and 20-31 under 35 USC 112, second parag. is withdrawn in view of Applicants amending the claims to remove "claim 0".
6. Claims 1-4, 6, 20-34, 42, 46-48 and 77-88 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods which use cardiac cells and wild-type Gem protein encoded by SEQ ID NO: 1, but not for all other excitable cells embraced by the claims, wherein the wild-type Gem protein blocks an L-type Ca^{2+} channel and wherein said blockage results in a shortening of a cardiac QT interval an/or reduction of the heart rate in atrial fibrillation. The claimed methods are not enabled for attenuating cardiac hypertrophy when using a W269G variant of the Gem protein.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass shortening of a cardiac QT interval and/or a reduction of the heart rate in atrial fibrillation in any excitable cell and using a W269G variant of the GEM protein encoded by the nucleic acid set forth in SEQ ID NO: 1.

Whereas the nature of the invention is a method of modulating cardiac cell calcium channels using a specific calcium handling protein, the skilled artisan would not find the claimed method enabled for its entire breadth. First, the claimed methods now require that the method results in a " shortening of a cardiac QT interval and/or a reduction of the heart rate in atrial fibrillation". However, the claims are drawn to any excitable cells and this is problematic since not all excitable cells are involved in the QT interval or heart rate. It is widely accepted that excitable cells are defined as any cell that can propagate an action potential because of their excitable membranes. The cells that can propagate an action potential are neurons, myocytes and electrocytes. Since the claims now require a shortening of a cardiac QT interval and/or a reduction of the heart rate in atrial fibrillation, not just any excitable cell will meet this claim limitation, rather only a cardiac cell, modulated by the contacted GEM protein will result in the new claim limitations.

The breadth of the claimed methods encompasses modulating, including blocking, activating or otherwise altering, the activity of an L-type Ca^{2+} channel. However a review of the art teaches that administering a GEM protein blocks the L-type Ca^{2+} channel rather than modulating its activity as broadly claimed. For example Murata et al. teach that GEM inhibits the trafficking of calcium channel α subunits to the plasma membrane resulting in a blockade of Ca^{2+} into the cell (pg. 398 col. 2, 2004, Cir. Res., Vol. 95, pgs. 398-405). Regarding this blockade, Ballipejalli teaches that GEM binds to the $Ca_v\beta$ subunit of the L-type Ca^{2+} channel thus blocking said subunit from binding to the $Ca_v\alpha_1$ subunit (pg. 337 col. 2 parag. 2, 2004, Cir. Res., Vol. 95, pgs. 337-339). It is widely accepted in the art that plasma membrane channels do not have an activity per se, rather channels only serve to transmit a molecule into or out of the cell. The activity is downstream effectors which gate the said channel to open or close as needed. In the instant case, the GEM protein is a downstream effecter which blocks the L-type Ca^{2+} channel from receiving a necessary subunit to permit extracellular Ca^{2+} from entering the cell. Further the claims recite modulating the activity of the L-type Ca^{2+} channel, which encompasses an increase or decrease in activity. However as the art teaches above, the GEM protein can only decrease extracellular Ca^{2+} influx into a cell, rather than increase its influx as embraced by the claims.

However, while the working examples teach that administration of human GEM resulted in phenotypes such as shortening of QT interval in guinea pigs and attenuating cardiac hypertrophy in mice, the phenotypes observed are due to the blockade of L-type Ca^{2+} channel and not just the modulating of L-type Ca^{2+} channel activity.

The working examples teach the shortening of a cardiac QT interval (Example 2) and a reduction of the heart rate in atrial fibrillation (Example 3) in guinea pigs that received a direct injection of an adenovirus encoding WT GEM (SEQ ID NO:1). The skilled artisan could not reasonably expect that an excitable cell such as a neuron of the brain or a myocyte present in the skeletal muscle of the foot would, when contacted with an adenovirus encoding a GEM protein

(SEQ ID NO: 1), shorten the QT interval and/or reduce heart rate. Thus the only excitable cell that would enable the claimed invention would be a cardiac myocyte.

Regarding the method of claim 47 for attenuating cardiac hypertrophy using naked DNA delivery of the W269G GEM variant, the art of record (and response to arguments below) has set forth that the claimed would be unpredictable (Non-Final office action mailed on 3/5/09, pages 3-9 and the Final Rejection mailed on 3/18/2010, pages 4-8). The art of record has established that using naked DNA delivery of the W269G mutant would be unpredictable for attenuating cardiac hypertrophy since each animal model taught varied results regarding reducing L-type calcium channel activity.

Applicant's Arguments

Applicants argue in amendment filed on 5/13/2010 that adenovirus delivery yields only 15- 25% transduction of excitable cells (Office Action, page 4). Applicants continue that Example 1 provides enabling disclosure (e.g., dose, route, methods, etc.) relating to the delivery of adenovirus vector that results in non-lethal levels of cellular GEM expression. Applicants continue that they have amended claim 47 to recite a method for attenuating cardiac hypertrophy by modulating the activity of a calcium channel in a predetermined region of excitable cells in a mammal using the W269G GEM variant which, as disclosed in Example 4 and Figure 5 of the specification, consistently attenuates indicia of cardiac hypertrophy.

Applicants conclude that the data disclosed in the specification demonstrates the consistent effect of the W269G GEM variant on cardiac hypertrophy, thereby addressing the Patent and Trademark Office's concerns regarding the alleged unpredictability of using the W269G variant.

Examiner's Reponses

Applicants argue that they have amended the claims to recite that only adenovirus comprising either WT GEM or the W269G GEM mutant will be used in the claimed methods. While this amendment does address the issue of enablement regarding naked DNA delivery (Final, 3/18/2010, pgs. 5-6) and a controlled 15%-25% transduction, the claimed method of attenuating cardiac hypertrophy remains unpredictable. Applicants argue that the working examples enable the claimed invention by consistently effecting cardiac hypertrophy using the W269G mutant.

A review of the working examples teaches that the delivery of the WT GEM shortened the QT interval (Example 2, pgs. 44), and caused a reduction of heart rate in atrial fibrillation (Example 3, pg. 45) in guinea-pigs as well as attenuation of cardiac hypertrophy (Example 4, pg. 46) in mice.

In contrast to the WT GEM, the W269G mutant in this example did not change the QT interval when used under the same conditions. The specification continues to teach that in a swine atrial fibrillation model GEM gene transfer to the swine heart via intracoronary perfusion resulted in prolongation of the PR interval monitored by surface EKG, the AH interval monitored by intracardiac electrogram and caused a 20% reduction in the ventricular rate during atrial fibrillation (pg. 45 Example 3).

Further an examination of the working examples as a whole presents a complex picture to the skilled artisan as how to determine the effectiveness the nucleic acid encoding a GEM protein. Each of Examples 1-4 demonstrates a different phenotype situation (that is dependent on calcium channel activity) and in each case the WT GEM protein and the W269G mutant differ in how they impact said phenotypes through calcium channel activity modulation. Collectively the working examples in view of the newly amended claims presents a situation of unpredictability regarding the enabled practice of the claimed method such that the skilled artisan could not predictably modulate the activity of a calcium channel in an excitable cell, particularly if attenuating cardiac hypertrophy is required and in some cases it's lethal.

The unpredictability of the working examples was previously addressed in view of the teachings in the art in the Final rejection mailed on 1/8/2010, pages 6-7:

"For example, Beguin et al. teach that the GTP-bound form of kir/GEM (a Ras-related small G-protein) inhibits high-voltage-activated calcium channel activity by interacting directly with the beta-subunit (pg. 701, Abstract). Beguin continues to teach that inhibition of L-type calcium channels by kir/GEM prevents calcium triggered exocytosis in hormone-secreting cells and propose that kir/GEM interacts with beta-subunits regulating calcium channel expression at the cell surface (pg. 701, Abstract, last four lines). Beguin summarizes that kir/GEM could have a protective effect against an overload of calcium (toxicity) that impairs a variety of cellular functions and may also inhibit cell proliferation by reducing calcium-mediated cell growth (pg. 705, col. 1 parag. 1, last four lines). However, while Beguin teaches that using GEM protein could have a protective effect against an overload of calcium, this protective effect is conditional as the working examples summarized above demonstrate. Using WT/full-length/or fully active GEM protein to modulate calcium channel activity is near total in its effectiveness to blockade calcium channel excitement".

As the art teaches above, the modulation of calcium channel activity is complex, and in the case of total calcium blockade a toxic outcome could be reasonably expected.

Conclusion

This issue of unpredictability regarding the claimed method is that the working examples present conflicting data regarding when and how the activity of a calcium channel is modulated using the W269G mutant. In some situations this is effective, in some situations its lethal and in some situations there is no effect at all. The skilled artisan cannot look to the art to overcome this unpredictability since the art supports that modulating calcium channel activity in a cell can be either protective or toxic to a cell and ultimately is situational. Collectively this presents to the skilled artisan that the claimed method of attenuating cardiac hypertrophy is unpredictable and that and undue amount of experimentation without a predictable degree of success is required to make and use the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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